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Dear Sir or Madam:

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The enclosed document is submitted pursuant to the TSCA Section 8(e) Compliance Audit Program and the CAP Agreement between Rohm and Haas Company and the Environmental Protection Agency. This document does not contain confidential business information.

The following is a summary of the contents of the submission under Unit II.C.3 of the CAP Agreement:

Tested Chemical:	Benzene, 1,3-diisocyanatomethyl-
CASRN:	26471-62-5
Title of Report or Study:	NTP Technical Report on the Carcinogenesis Bioassay of Toluene Diisocyanate (Report No. 82RN-1017)
Reportable Effect:	Carcinogenic in female mice.

If additional information is required, please contact the undersigned at (215) 592-3139. Thank you.

Sincerely,

Ronald L. Keener

Ronald L. Keener, Ph.D.
Regulatory Affairs Director
Product Integrity Department

RLK:so
Enclosure

82RN-1017

Jerry Smith
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Spring House Pa 19477

Toluene Diisocyanate Board of Scientific Counselors 9/22/82

NTP TECHNICAL REPORT

ON THE

CARCINOGENESIS BIOASSAY

OF

RN

~~83RJ-17~~

TOLUENE DIISOCYANATE

DRAFT

(86% 2,4-ISOMER and 14% 2,6-ISOMER)

(CAS NO. 26471-62-5)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDY)

Michael P. Dieter, Ph.D.
Chemical Manager

Prepared for Board of Scientific Counselors Meeting
9/22/82

NATIONAL TOXICOLOGY PROGRAM
P. O. Box 12233
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and
Bethesda, Maryland 20205

NOTICE

This is not a final report. Until this DRAFT is reviewed and approved by the Technical Reports Review Subcommittee of the NTP Board of Scientific Counselors, this DRAFT does not represent the official position of the National Toxicology Program.

DRAFT

NTP-82-2
NIH Publication No. 82-2507

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

TR No 251

NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of chemically induced disease. By bringing together the relevant programs, staff, and resources from the U.S. Public Health Service, DHHS, the National Toxicology Program has centralized and strengthened activities relating to toxicology research, testing and test development/validation efforts, and the dissemination of toxicological information to the public and scientific communities and to the research and regulatory agencies.

The NTP is comprised of four charter DHHS agencies: the National Cancer Institute, National Institutes of Health; the National Institute of Environmental Health Sciences, National Institutes of Health; the National Center for Toxicological Research, Food and Drug Administration; and the National Institute for Occupational Safety and Health, Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS.

NOTE TO THE READER

This is one in a series of experiments designed to determine whether selected chemicals produce cancer in animals. Chemicals selected for testing in the NTP carcinogenesis bioassay program are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical is a potential hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

This study was initiated by the National Cancer Institute's Carcinogenesis Testing Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program.

Comments and questions about the National Toxicology Program Technical Reports on Carcinogenesis Bioassays should be directed to the National Toxicology Program, located at Room A-306, Landow Building, Bethesda, MD 20205 (301-496-1152) or at Research Triangle Park, NC 27709 (919-541-3991).

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to communicate any mistakes to the Deputy Director, NTP (P.O. Box 12233, Research Triangle Park, NC 27709), so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP.

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650).

Single copies of this carcinogenesis bioassay technical report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

TABLE OF CONTENTS

TABLES

Page

FIGURES

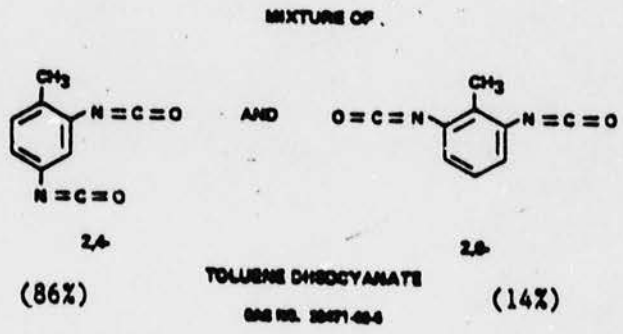
APPENDIXES

APPENDIXES (Continued)

APPENDIXES (Continued)

APPENDIXES (CONTINUED)

ABSTRACT



Groups of 50 female F344/N rats and 50 female B6C3F$_1$ mice were administered toluene diisocyanate in corn oil by gavage at doses of 60 or 120 mg/kg body weight, 5 days per week for 105 or 106 weeks. Groups of 50 male F344/N rats received 30 or 60 mg/kg and groups of 50 male B6C3F$_1$ mice received 120 or 240 mg/kg on the same schedule. Groups of 50 rats and 50 mice of each sex received corn oil only and served as vehicle controls.

Survival in all groups of dosed rats in the 2-year study was significantly shorter ($P \leq 0.005$) than that of the controls; depressions in mean body weight gain relative to controls were greater than 10% in all dosed rat groups throughout most of the study. A dose-dependent pattern of cumulative toxicity began at 70 weeks which culminated in excessive mortality.

Subcutaneous tissue fibromas or fibrosarcoms (combined) in male rats occurred with a statistically significant trend ($P \leq 0.007$; control, 3/50, 6%; low-dose, 6/50, 12%; high-dose, 12/50, 24%). The incidence in the high-dose group was significantly higher than that in the controls ($P \leq 0.011$). The same tumor comparisons were significant ($P < 0.001$) in female rats by the life table analysis.

Pancreatic acinar-cell adenomas in male rats occurred with a statistically significant trend ($P \leq 0.020$; control, 1/47, 2%; low-dose, 3/47, 6%; high-dose, 7/49, 14%). The incidence in the high-dose group was significantly higher than that in the controls ($P \leq 0.034$).

The incidences of pancreatic islet-cell adenomas in female rats were significantly higher by the incidental tumor test ($P \leq 0.010$) in low-dose (6/49, 12%) and high-dose (2/47, 4%) groups than in controls (0/50). An islet-cell carcinoma was also observed in a low-dose female rat.

The incidences of female rats with neoplastic nodules in the liver occurred with a statistically significant positive trend ($P \leq 0.035$; control, 3/50, 6%; low-dose, 8/50, 16%; high-dose, 8/48, 17%), and the incidence in the high-dose group was significantly higher ($P \leq 0.022$) than that in the controls by the life table and incidental tumor tests.

Mammary gland fibroadenomas in female rats occurred with a statistically significant trend (P 0.001), and the incidences in low- and high-dose groups were significantly higher than that in controls (P 0.01) by the incidental tumor test.

Rare brain tumors, two gliomas and a pinealoma, were found in three high-dose male rats. The incidence of all types of brain tumors found in the Bioassay Program is 10/995.

Acute bronchopneumonia occurred at increased incidences in groups of dosed male and female rats (males: control, 2/50, 4%; low-dose, 6/50, 12%; high-dose, 14/50, 28%; females: control, 1/50, 2%; low-dose, 10/50, 20%; high-dose, 25/49, 51%).

Survival of high-dose male mice in the 2-year study was significantly shorter than that of the controls ($P<0.001$). During the second year of the study, mean body weight gains of high-dose male mice were less than those of the controls.

Hemangiomas or hemangiosarcomas (combined) of the circulatory system in female mice occurred with a statistically significant trend ($P \leq 0.011$; control, 0/50, 0%; low-dose, 1/50, 2%; high-dose, 5/50, 10%). The incidence in the high dose group was significantly higher than that in the controls ($P \leq 0.029$).

Hepatocellular adenomas in female mice occurred with a statistically significant positive trend ($P \leq 0.001$; control, 2/50, 4%; low-dose, 3/50, 6%; high-dose, 12/50, 24%), and the incidence in the high-dose group was significantly higher than that in the controls ($P \leq 0.004$).

Cytomegaly of kidney tubular epithelium was found in 45/48 (94%) low-dose male mice and 41/50 (82%) high-dose male mice but not in any of the controls.

Under the conditions of this bioassay, toluene diisocyanate was carcinogenic for F344/N rats, causing subcutaneous fibromas and fibrosarcomas (combined) in males and females, pancreatic acinar-cell adenomas in males, and pancreatic islet-cell adenomas, neoplastic nodules of the liver, and mammary gland fibroadenomas in females. Toluene diisocyanate was carcinogenic for female B6C3F$_1$ mice, causing hemangiomas or hemangiosarcomas (combined), as well as hepatocellular adenomas, but it was not carcinogenic for the male mice.

CONTRIBUTORS

The bioassay of toluene diisocyanate was conducted at Litton Bionetics, Inc. under a subcontract to Tracor Jitco, Inc., the prime contractor for the Carcinogenesis Testing Program. The two-year study was begun in December 1978 and completed in January 1981

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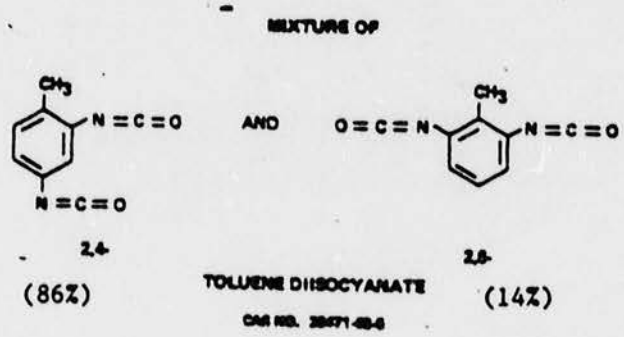
The chemicals used in this bioassay of tol... ...anates were analyzed by the Midwest Research Institute, 425 Volker ... Kansas City, Missouri 64110, and reanalysis of the bulk chemical ... ...mical/vehicle analyses were done by Litton Bionetics, Inc.

I. INTRODUCTION



Toluene diisocyanate (TDI) is commercially produced as an approximate 80:20 mixture of the 2,4- and 2,6-isomers. In 1980, 580,000 pounds of this chemical were produced in the United States, primarily for use in the manufacture of flexible polyurethane foams (USITC, 1981). These foam elastomers are found in furniture and automobile cushions, carpet underlays, pillow filling, mattresses, insulation, shoes, purses, and toys (Kirk-Othmer, 1970). TDI is also used to produce polyurethane coatings for lacquers and wood finishes (IARC, 1979).

TDI reacts readily with polyols, water, urea, urethanes, amines, and other basic compounds (E.I. DuPont, 1969; Ehrlicher, 1974). Concentrations as high as 10 ppm TDI have been measured in the air above urethane foams during their production (Buist, 1970). The maximum allowable 8-hour time weighted average concentration of 2,4-toluene diisocyanate to which workers can be exposed is 0.02 ppm (U.S. CFR, 1974).

The oral LD_{50} value for TDI in rats is 5.8 g/kg body weight (Zapp, 1957), and the LC_{50} values for rats and mice are 14 and 10 ppm, respectively (Duncan, 1962).

No information has been found on the metabolism of TDI.

Skin, eye, and respiratory tract irritation has been reported in both humans and rats exposed to TDI in air (Union Carbide, 1976; Patty, 1963). Hypersensitivity to TDI, manifested as an asthma-like response, has been reported in workers exposed to the chemical (Parkes, 1970; Taylor, 1970; Sangha and Alarie, 1979), and a 10-hour TWA exposure concentration of 5 ppb TDI has been recommended for workplace air (NIOSH, 1979).

Both 2,4- and 2,6-diaminotoluene were mutagenic in Salmonella typhimurium TA 1538 (Dybing and Thorgeirsson, 1977; Andersen et al., 1980). Although 2,4-toluene diisocyanate was reported as not mutagenic in S. typhimurium TA 1535, TA 1538, TA 98, and TA 100, with or without metabolic activation with S-9 preparation from Aroclor-1254 induced Sprague-Dawley rats (Anderson and Styles, 1978), an 80:20 mixture of 2,4- and 2,6-toluene diisocyanate was mutagenic in a narrow dose range in S. typhimurium TA 100, TA 98, and TA 1538 after metabolic activation with rat liver S-9 preparation from phenobarbital-induced rats (Andersen et al., 1980). Differences in the results from the two studies are probably due to differences in the test conditions.

The Bioassay Program tested a commercial TDI mixture since a large number of workers (approximately 40,000) are potentially exposed to these isomers and because no long-term studies were available.

IV. DISCUSSION AND CONCLUSIONS

TDI reacted with the moisture in the corn oil vehicle, reducing the doses received by rats and mice in the 2-year studies to 10% to 23% below the target doses. Despite the reduced doses, mean body weight gains of male and female rats were less than those of the controls after week 30. Early deaths occurred in groups of dosed male and female rats, but by week 60 only the high-dose male rats were dying as a result of TDI administration. At this time, a decision was made to continue the bioassay of rats; however, an apparent dose-related pattern of mortality began to emerge at week 70, and it persisted until the end of the study. Mortality in mice was also dose related and significantly higher than in controls, but it was not as excessive as that in rats. The delayed cumulative toxicity caused by TDI administration indicated that maximum tolerated doses had been exceeded in rats and that they had been exceeded, though to a lesser extent, in mice.

Bronchopneumonia was the most prominent nonneoplastic effect seen in the short-term and 2-year phases of this bioassay. The respiratory effects observed were similar to those seen in rats exposed by inhalation to TDI at a concentration of 0.1 ppm for 6 hours per day, once per week, for 38 weeks: tracheitis, bronchitis, pneumonia, and purulent bronchiectasis (Niewenhuis et al., 1965).

TDI stimulates the trigeminal nerve and is one of the more potent sensory irritants (Sangha and Alarie, 1979). Occupational asthma, or reversible obstruction of the airways in response to TDI, has been seen in workers exposed to the chemical (Weil et al., 1981). Workers exposed to TDI at

concentrations of less than 0.1 ppm had marked declines in forced respiratory volume, with reductions in the ratio of forced expiratory volume to forced vital capacity; forced expiratory flow was 25%-50% of the forced vital capacity. Bronchial hypersensitivity to TDI developed in 4.3% of these workers, but there were no predictive indices for this response. Respiratory hypersensitivity has been shown to develop in guinea pigs exposed to 0.005 ppm TDI after dermal contact with the chemical (Karol et al., 1981).

The late-appearing pattern of mortality in rats in the present study is consistent with delayed hypersensitivity. The incidences of bronchopneumonia were dose related in male and female rats, and this effect probably weakened the animals' resistance to further chemical challenge. The increased rate of mortality may also be due, in part, to TDI's inhibition of acetylcholinesterase, which could have compounded the animals' respiratory difficulty (Brown et al., 1982). The study by Brown and coworkers showed that 2,6-toluene diisocyanate was 60 times more effective than the 2,4-isomer in inhibiting human serum cholinesterase. The commercial mixture of TDI used in the present bioassay consisted of 86% 2,4-isomer and 14% 2,6-isomer, the latter being the active enzyme inhibitor.

Despite the reduced survival, there was unequivocal evidence of dose-related increases in tumors in rats and mice in the 2-year study. About 50% of the tumors detected were observed in animals killed at the end of the study; the rest were found in animals dying between weeks 77 and 108. The digestive

system was the primary site of tumor induction, and the tumors found included acinar-cell adenomas of the pancreas in male rats, islet-cell adenomas of the pancreas in female rats, and liver tumors in female rats and mice. In rats, dose-related increases were observed in the number of males with nodular hyperplasia of the pancreatic acinus (control, 0%; low-dose, 4%; high-dose, 8%) and with acinar-cell adenomas (control, 2%; low-dose, 6%; high-dose, 14%), suggesting that these nodules were preneoplastic in nature. The systemic nature of the carcinogenicity of TDI was demonstrated by the appearance of tumors at multiple sites in male rats (fibromas and fibrosarcomas) and female mice (hemangiomas and hemangiosarcomas).

The tumors observed in the liver, pancreas, mammary gland, and subcutaneous tissues of F344/N rats in this study are similar to those seen when 2,4-diaminotoluene -- an hydrolysis product of 2,4-toluene diisocyanate -- was administered to the same strain (NCI, 1979). In the 2,4-diaminotoluene study, increased incidences of neoplastic nodules and hepatocellular carcinomas were found in males fed 79 or 176 ppm and in females fed 171 ppm. Increased incidences of pancreatic acinar-cell adenomas were observed in dosed males and in females that received 171 ppm. The incidences of mammary gland fibroadenomas in females were 10-fold greater in the low- and high-dose groups compared with controls. Furthermore, subcutaneous fibromas were found at significantly increased incidences relative to controls in dosed male rats.

In addition, 2,4-diaminotoluene causes increases in hemangiomas and hemangiosarcomas in male mice and significant increases in hepatocellular neoplasms in both sexes of mice. Although TDI caused the same neoplasms in the present study, they were restricted to female mice. There are no available metabolic data that might account for the difference in response between these tests. The hydrolysis product of 2,6-toluene diisocyanate (2,6-diaminotoluene) was not carcinogenic for F344/N rats and B6C3F$_1$ mice (NTP, 1980).

Other noteworthy effects observed in rats in the current study included the brain tumors found in males (two had gliomas and one had a pinealoma). Gliomas have been found in 3/995 controls in the bioassay program and pinealomas have not been previously diagnosed (Appendix J, Table J9). The evidence suggests an association between these tumors and administration of TDI.

Differences in mean body weight gains, hypersensitivity, and the incidences of neoplastic and nonneoplastic lesions in animals in the present study emphasize differences in the degree to which TDI is toxic in different species and sexes. Both female rats and female mice received doses of 60 or 120 mg/kg, and most of the rats died during the study. Male mice received higher doses (120 and 240 mg/kg) than male rats (30 and 60 mg/kg), yet mortality and decreases in mean body weight gain were less severe in the former group, and no tumors were detected at statistically significant incidences in the mice. Male and female rats and female mice showed

positive evidence of the carcinogenicity of TDI. The species and sex differences in sensitivity to TDI may be metabolic, but no experimental data are available.

By contrast, a private communication reported by Woolrich (1982) states that there were no compound-related increases in the incidence of tumors in rats (unspecified strain) exposed by inhalation for 113 weeks to 0.05 and 0.15 ppm TDI. No written report is available for confirmation.

There are also conflicting reports about the mutagenicity of TDI. Anderson and Styles (1978) originally reported that 2,4-toluene diisocyanate of unknown purity was non-mutagenic in a study of 120 chemicals performed by Purchase et al. (1978), but several known mutagens were also reported as negative, suggesting a lack of definition in these studies. Andersen et al. (1980) later optimized the procedure for testing volatile isocyanates, and in a study with adequate positive and negative controls showed that a mixture of 2,4- and 2,6-toluene diisocyanate (Desmodur T80) caused a dose-dependent mutagenic response utilizing S-9 activation in Salmonella typhimurium strains TA 98, TA 100, and TA 1538. The positive control was 2,4-diaminotoluene, the hydrolysis product of 2,4-toluene diisocyanate, which Ames et al. (1975) reported to be mutagenic.

A gavage test with 4,4'-diphenylmethane diisocyanate (MDI) was recently deferred by NTP because of problems similar to those encountered here — difficulties with dose preparation and unexplained toxicity in the

prechronic studies. For an adequate examination of the toxic reponses to this class of chemicals, particularly to define the metabolism and to evaluate the biochemical and immunological toxicity, it would be necessary to conduct further tests at lower dose levels. Such a comparison of the toxicological properties of TDI, MDI, and other commercially important isocyanates in polyurethane production would be useful, since annual production of these exceeds 1 million tons (Sangha and Alarie, 1979) and only limited toxicological information is available (Woolrich, 1982). It would be preferable to test these chemicals by the inhalation route, since potential human exposure occurs during their production (Weil et al., 1981) or during fires, when the pyrolysis products of polyurethanes are released. Woolley and Raftery (1976) stated that the yellow smoke released during decomposition of flexible polyurethane foam at 200°-300°C appeared to be a polymerized form of TDI. In another study, results of gas chromatographic analysis and mass spectrometry indicated that toluene monoisocyanate was the major decomposition product from combustion of flexible polyurethane foams (Alarie et al., 1975). A report on the occupational hazards of firefighting specifically cites the dangers of exposure to isocyanates produced from the combustion of polyurethane or encountered as neat chemical (Axford et al., 1976).

In summary, the commercial mixture of 2,4- and 2,6-toluene diisocyanate has been shown to produce a variety of toxic effects in humans and animals, including asthma, decreased respiratory function, delayed pulmonary hypersensitivity, bronchopneumonia, and inhibition of acetylcholinesterase.

The hydrolysis product (2,4-diaminotoluene) of the 2,4-isomer and the mixture of the 2,4- and the 2,6-isomers of TDI have been shown to be mutagenic. In the present study, the pattern of multifocal proliferating tumors was similar to the carcinogenic responses produced by the hydrolysis product of the 2,4-isomer.

Under the conditions of this bioassay, toluene diisocyanate was carcinogenic for F344/N rats, causing subcutaneous fibromas and fibrosarcomas (combined) in males and females, pancreatic acinar-cell adenomas in males, and pancreatic islet-cell adenomas, neoplastic nodules of the liver, and mammary gland fibroadenomas in females. Toluene diisocyanate was carcinogenic for female B6C3F$_1$ mice, causing hemangiomas or hemangiosarcomas (combined) as well as hepatocellular adenomas, but it was not carcinogenic for the male mice.

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